Macromolecular Research
https://doi.org/10.1007/s13233-023-00141-w

Online ISSN 2092-7673
Print ISSN 1598-5032

REVIEW

Bioadhesives based on multifunctional biopolymers for biomedical applications

Seoyoon Yu[1,2] · **Chaenyung Cha**[1]

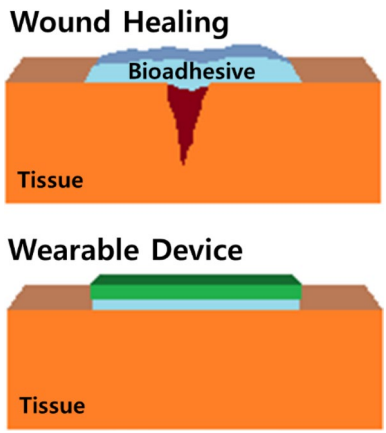
Received: 11 January 2023 / Revised: 8 February 2023 / Accepted: 12 February 2023

Abstract

With the recent advancement in emerging biomedical engineering fields, such as tissue engineering, regenerative medicine, and wearable medical devices, there is a growing need to develop adhesives that can function not only as tissue sealants for surgery and wound closure, but also attach various biomaterials and devices. These "bioadhesives" should allow refined control of cohesive and adhesive properties, while significantly improving the biocompatibility and biodegradability. For this reason, bioadhesives are being developed using a wide range of natural biopolymers with proven biocompatibility that can also impart multifunctionality either using their innate properties and/or obtained via various chemical modifications. In this review, state-of-the-art bioadhesives made from multifunctional biopolymers are introduced.

Graphical abstract

Natural biopolymers are increasingly utilized to develop adhesives for biomedical applications, including wound healing and biomedical devices, for their favorable physicomechanical properties as well as their proven biocompatibility. Furthermore, various modification strategies are often employed to impart multifunctionality. In this review, recent development and notable examples of bioadhesives based on multifunctional biopolymers are highlighted.



Keywords Bioadhesive · Biopolymer · Biocompatibility · Adhesion · Cohesion · Biodegradation

✉ Chaenyung Cha
ccha@unist.ac.kr

[1] Department of Materials Science and Engineering, Center for Multidimensional Programmable Matter, Ulsan National Institute of Science and Technology (UNIST), 50 UNIST-gil, Ulju-gun, Ulsan 44919, Korea

[2] Center for Advanced Specialty Chemicals, Korea Research Institute of Chemical Technology, Ulsan 44412, Korea

1 Introduction

A diverse array of polymers has been utilized to develop adhesives for biomedical applications. These "bioadhesives" refer to the materials that have sufficient adhesive strength towards the surfaces of biomaterials, such as hydrogels, nanofibers, nano- and micro-particles, as well as biological

Published online: 05 April 2023

tissues [1–4]. Bioadhesives are increasingly implemented in emerging biomedical fields, such as surgical and wound closure (tissue sealant), implant fixture (e.g. dental and bone), drug delivery systems, and wearable bioelectronics. There is a growing need to develop bioadhesives with much improved adhesive properties, biocompatibility and production efficiency, as the next generation of biomedical engineering is likely to involve the use of biomaterials developed from various sources [5]. The bioadhesives will ensure their simplified operation, reduce surgical time and minimal invasiveness.

The most important distinction for bioadhesives is the requirement for biocompatibility. This is the primary reason for utilizing natural biopolymers, such as polysaccharides and proteins. But synthetic polymers with proven biocompatibility are also widely utilized. Hemotoxicity and cytotoxicity are considered gold standard for in vitro evaluation of the biocompatibility, as outlined by International Organization for Standardization (ISO) 10993. For more detailed and physiological analyses, animal models are also used. These in vivo analyses can provide in-depth systemic responses, such as inflammation, immunogenicity and wound healing, in addition to measure adhesion strength against biological tissue.

Similar to other adhesives, bioadhesives require a delicate balance between cohesion and adhesion [6, 7]. Strong adhesion is based on the ability to safely induce chemical and/or physical bonds between the adhesive material and the surface of biomaterial. This is especially challenging, because most biomaterials and tissues contain significant amount of water, which generally opposes strong adhesion to the surface. Therefore, the type of polymer and the mode of crosslinking must be carefully chosen. The cohesion, which refers to the mechanical strength of bioadhesives to withstand external forces without structural disintegration, can be controlled by controlling the degree of crosslinking. Additionally, other strategies for mechanical augmentation, such as interpenetrating network (IPN), semi-IPN, and nanocomposite formation, have been also employed [8, 9]. Generally, increasing cohesion improves adhesion by holding the adhesive molecules together, thereby opposing structural disintegration. However, further increase in cohesion beyond a critical limit diminishes the adhesion, because more adhesive molecules interact with each other at higher crosslinking density than those interacting with the surface [10]. Also, increasing cohesion could lead to increased brittleness and loss of ductility.

Compared to adhesives for industrial uses that require extremely high mechanical strength (e.g. assembly of machine parts and construction materials), the requirement for mechanical strength of bioadhesives is not as stringent, since they are mostly subjected to mild and transient stress. Nonetheless, they should be able to withstand external forces generated post application in such cases as various natural bodily movements. More importantly, as many biomaterials and biological tissues are highly flexible in nature, it would be ideal for the bioadhesives to match their elastic mechanical properties to prevent mechanical failure by mechanical mismatch. For example, it has been reported that brain tissue is generally very soft, with the Young's modulus of 1 kPa or lower, while that of precalcified bone tissue can reach up to a hundred kPa [11]. For this reason, and given the fact that most biopolymers are only aqueous-soluble, most bioadhesives are in the form of hydrogel by sol–gel transition of the biopolymer solution, and there is added emphasis placed on the ability to control their mechanical properties by controlling the crosslinking density. Natural biopolymers generally lack the mechanical strength compared to synthetic polymers, so chemical modification to impart various functional groups is often applied to biopolymers to allow more robust and controllable chemical crosslinking. Furthermore, this makes it possible to hybridize different polymer systems in order to introduce added functionalities.

Bioadhesives based on natural polymers often rely on physical interactions, mostly hydrophobic interaction, hydrogen bonding, and ionic interactions. Therefore, the 'physical adhesion' has the advantage of controlling both adhesion and cohesion using the inherent physicochemical properties of the natural polymers. In addition, it is also highly desirable for bioadhesive to be injectable, as the liquid precursor solution can undergo spontaneous curing ("in situ forming") upon application with proper stimuli such as temperature and pH. However, these interactions are generally weaker than 'chemical adhesion' which involves a wide range of chemical reactions to induce linkage to the material surface for adhesion as well as chemical crosslinking to control the cohesion. The chemical adhesion is broadly applicable to both natural and synthetic polymers, as reactive functional groups capable of undergoing chemical crosslinking can often be presented to polymers [12, 13]. But for the sake of maintaining the biocompatibility, the reaction conditions must be carefully chosen that they are able to proceed without causing significant harm to the host. The chemical reactions that can proceed under physiological conditions without causing significant toxicity, such as Michael addition, Schiff base formation, and "click" chemistry, as well as those mediated by enzymes, are also widely used to create in situ forming bioadhesives.

For bioadhesives intended for temporary implantation like surgical glues, which is used in place of or to augment sutures in our body, it is highly desirable for them to undergo biodegradation in order to avoid additional surgical procedure to remove them. Many protein-based bioadhesives, including gelatin and fibrin, have the advantage in this case due to the abundance of protein-degrading enzymes (i.e. proteases) [14, 15]. An important consideration for the

development of biodegradable bioadhesives is balancing the rate of biodegradation while not compromising their mechanical integrity. Obviously, the destruction of polymer chains during the biodegradation process inevitably leads to the loss of cohesion, which in turn leads to the loss of adhesion. This is especially problematic for protein-based bioadhesives which often suffer from premature biodegradation. Therefore, it is important to design the biodegradable bioadhesives to maintain their cohesion and adhesion until sufficient wound healing and tissue regeneration have taken place. Furthermore, the degraded byproducts must not cause significant inflammation to the surrounding tissue.

With these characteristics and considerations for bioadhesives in mind, considerable research efforts are underway to develop the next-generation bioadhesives, some of which have already been approved for use. In the following, bioadhesives based on various natural polymers are introduced with several notable examples.

2 Polysaccharide-based bioadhesives

Polysaccharides such as alginate, chitosan, dextran, and cellulose, have long been a fixture in biomedical engineering. They are commonly used to fabricate nanofibers and hydrogels for drug delivery and tissue engineering applications [16–18]. Due to their highly tunable viscoelastic properties in solutions, they are widely used as additives for food and drug manufacturing. They have the critical advantage of abundant natural source (e.g. agricultural feedstock and seaweed) and biocompatibility. Some even undergo natural gelation by physical interactions. For example, anionic polysaccharides such as alginate and κ-carrageenan undergo ionic crosslinking to form hydrogels using divalent ions. Agarose solution undergo temperature-dependent sol–gel transition via hydrogen bonding. Polysaccharides have numerous hydrophilic functional groups, which are often chemically modified to change their physical and chemical properties in order to control their viscoelastic properties and provide additional crosslinking sites. Hydrogels made from polysaccharides are heavily being investigated for use as bioadhesives for surgical sealant, as they can provide both barrier against harmful external environment and moisture for tissue hydration. They are especially highly swellable due to the hydrophilic nature of polysaccharides, which allows the absorption of bodily fluids from wound sites.

Highly viscous nature of polysaccharide solutions also results in higher "tack", which can be described as the instant bonding, or stickiness, of an adhesive to a surface. Since chemical bonds between the adhesive and the surface take time to form, tack is mostly governed by the physical bonds that form instantaneously upon contact. Therefore, higher tack is observed for polysaccharides capable of extensive hydrogen bonding and hydrophobic interaction. Having higher tack is often desired if there is a concern of slow curing time, in which the solution may uncontrollably flow to undesired areas.

Even though some of the polysaccharides can undergo physical crosslinking, it is still difficult to precisely control their mechanical properties. Therefore, it is now more common to employ chemical crosslinking schemes to polysaccharides for greater maneuverability. For example, Li et al. developed a photocrosslinkable dextran bioadhesives by conjugating methacrylic functional groups to dextran via urethane bond ('Dex-U') [19]. The degree of substitution (DS) of methacrylic groups of Dex-U could be conveniently controlled by the amount of reactant, isocyanatoethyl methacrylate, and the low cytotoxicity also indicated that the chemical modification did not negatively affect the biocompatibility. The maximum adhesion strength against gelatin substrate, measured by the lap-shear test, was nearly 3 MPa, which was 47 times higher than that of a commercial bioadhesive. As a follow-up, Wang et al. introduced biodegradability and secondary crosslinking to Dex-U by partial oxidation of dextran by periodate to generate hydrolysable hemiacetal groups and aldehyde groups capable of additional crosslinking via Schiff base formation. [20]

For minimally invasive application, it is desirable for the bioadhesives to be cured upon injection of the liquid precursor. Olivia et al. developed a syringe-injectable bioadhesive consisting of oxidized dextran and dendrimeric polyamidoamine (PAMAM) via Schiff base formation (Fig. 1) [21]. The adhesion strength and the extent of interaction between the bioadhesive and tissue surface increased with the dextran concentration. This result indicated that aldehyde in oxidized dextran could also undergo Schiff base formation with numerous amine groups present in tissue surface, leading to stronger adhesion. Giano et al. have similarly reported a bioadhesive consisting of oxidized dextran (i.e. polydextran aldehyde (PDA)) and branched polyethylenimine (PEI) [22]. At a given PDA concentration of 2.5 wt%, the storage modulus was controlled from 640 to 4350 Pa, and the maximum adhesive strength was controlled from 1.83 to 2.76 kPa, by the PEI concentration from 3.5 to 10.3 wt%. This result clearly indicated that this material system allowed the significant control of cohesion without compromising the adhesion. In addition, the range of modulus was on par with that of biological tissues. Due to the inherent antibacterial properties of PEI, owing to numerous amine groups, the PDA-PEI bioadhesive demonstrated substantial antibacterial activity.

Unlike dextran which is charge-neutral, chitosan is a cationic polysaccharide derived from chitin, which is also a polysaccharide consisting of N-acetyl-$_D$-glucosamine (GlcNAc) units. It is the second most abundant natural polysaccharide, next to cellulose, as it is the major

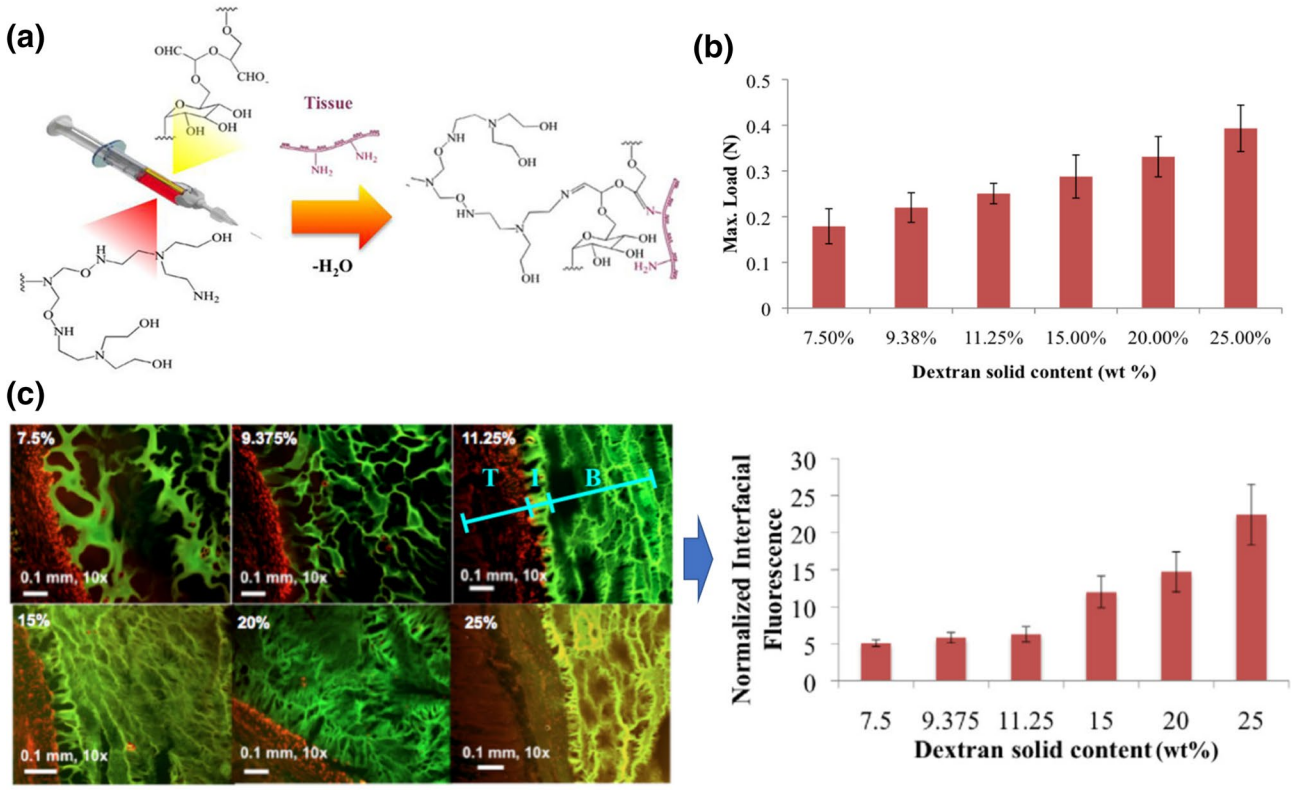


Fig. 1 **a** Schematic illustration of an injectable hydrogel bioadhesive by crosslinking dendrimeric polyamidoamine (PAMAM) and oxidized dextran via Schiff base formation. **b** The maximum adhesion strength of the PAMAM/dextran bioadhesive against tissue increased with dextran concentration. **c** The degree of PAMAM/dextran bioadhesive interaction with tissue increased with dextran concentration. Reproduced with permission from Ref. [21]. Copyright © 2012 American Chemical Society

structural component of crustaceans and insects. Similar to plant-derived cellulose, chitin exists in a physically crosslinked form with high mechanical strength due to extensive hydrogen bonding through hydroxyl and acetyl amide groups. However, its insolubility in limits the broad applicability. Chitosan is an acid-soluble form derived from chitin by deacetylation of GlcNAc to $_{D}$-glucosamine (GlcN). Like other polysaccharides, chitosan is also biocompatible, biodegradable, and tunable viscoelastic solution properties, which allows the broad applicability in many food and drug formulations [23, 24]. The cationic nature of chitosan, owing to the numerous amine groups from GlcN, gives rise to highly unique physical properties [25]. Chitosan can be crosslinked multivalent anions, such as sodium tripolyphosphate (TPP), sodium hexametaphosphate (HMP), and trisodium citrate, to become hydrogels, while various chemical crosslinking methods can be applied for greater controllability by conjugating reactive functional groups. It is also widely recognized for natural antibacterial properties, as the cationic charge has been known to disrupt the bacterial cell wall. In addition, chitosan has also demonstrated mucoadhesive and hemostatic properties via electrostatic interaction with anionic mucin and cell membrane. All these factors have contributed to the popularity of chitosan as a bioadhesive material.

Chitosan is only soluble in acidic aqueous media, so chemical modification of chitosan is often used to enhance the biocompatibility by rendering chitosan soluble in neutral and basic aqueous media. For example, Kim et al. developed a poly(ethylene glycol) (PEG)-grafted chitosan hydrogel crosslinked by PEG-dialdehyde as an injectable bioadhesive (Fig. 2) [26]. Hydrophilic PEG rendered chitosan soluble in neutral and basic pH, while the crosslinking reaction via Schiff base formation proceeded under physiological conditions. The adhesion strength could be controlled by the crosslinking density and the PEG graft architecture (length and density), while all conditions demonstrated antibacterial properties. Furthermore, encapsulation of epidermal growth factor into the bioadhesive facilitated the wound healing and reduced scar formation, demonstrated using an in vivo skin wound model.

In addition to tissue sealant for wound healing, mucoadhesive properties of chitosan is also being investigated as a drug delivery system through mucosal administration [27]. This is especially an attractive area of biomedical application for chitosan, since chitosan nano- or micro-particles can

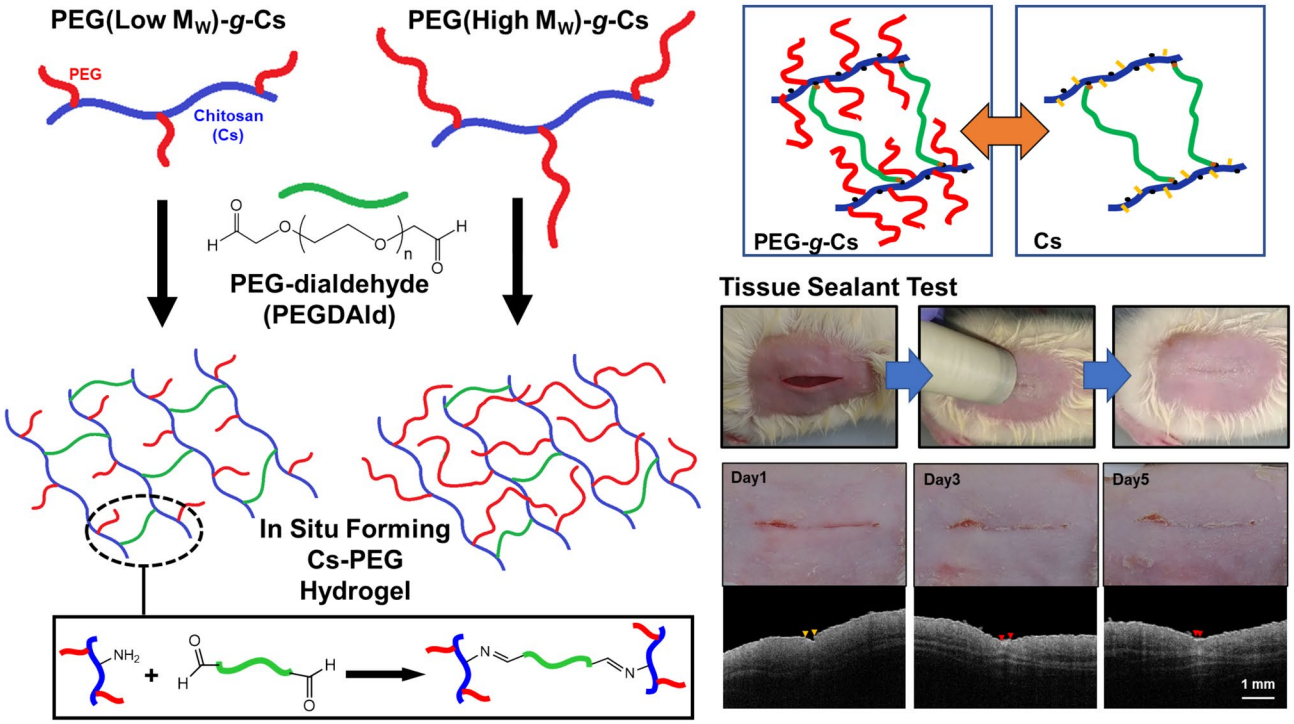


Fig. 2 PEG-grafted chitosan (PEG-g-Cs) is crosslinked by PEG dialdehyde via Schiff base formation to form Cs-PEG hydrogel bioadhesive. The mechanical and adhesive properties of the Cs-PEG hydrogel was controlled by crosslinking density and the PEG graft architecture. Cs-PEG as a tissue sealant was demonstrated using an in vivo skin wound model. Reproduced with permission from ref.[26]. Copyright © 2019 Elsevier Ltd

be easily formed by coacervation and ionic crosslinking of chitosan emulsion, and administered in a minimally invasive manner. For example, Sang et al. demonstrated that chitosan nanoparticles crosslinked by phytic acid (PA) showed higher drug encapsulation efficiency and mucoadhesiveness and slower drug release than those crosslinked by TPP and HMP [28]. In addition, chitosan can be incorporated into other types of materials to impart mucoadhesiveness. Tan et al. applied the surface coating of chitosan onto lipid nanocarrier containing amphotericin B, an antifungal drug [29]. In vivo studies have demonstrated that the orally administered, chitosan-coated nanocarrier showed much improved bioavailability than the non-coated control. This result was due to the prolonged transit and retention within the small intestine through mucoadhesion and subsequent absorption by the lymphatic pathway.

Even though chitin is not generally soluble in any solvent, chitin can be processed into nanoparticles and nanofibers which have been used as bioadhesives. For example, Hao et al. developed chitin nanoparticles functionalized with guanidinium as a bioadhesive [30]. The guanidinium moieties allowed multifaceted physical interactions, ionic interaction, hydrophobic interaction and hydrogen bonding, towards biological tissues. Whereas most biopolymer-based bioadhesives demonstrate gradual loss in adhesive strength under wet conditions mainly due to swelling, the chitin nanoparticle-based bioadhesive maintained stable adhesion against hydrated environment.

Catechol has been one of the most widely utilized functional groups for adhesives, as it was found to be the major mediator of adhesion of several species, such as mussel and gecko, through various physical and chemical pathways (Fig. 3) [31–33]. Therefore, many bioadhesives research efforts have adopted this "bio-inspired" approach by introducing catechol groups to control the adhesion. Chitosan has been especially attractive for catechol conjugation due to the abundant presence of chemically labile amine groups. Park et al. synthesized catechol-presenting chitosan ('C-CC') by conjugating 3,4-dihydroxyhydrocinnamic acid to chitosan via carbodiimide coupling [34]. Furthermore, catechol was converted to *o*-quinone derivative via enzymatic oxidation ('E-CC'). Since E-CC could promote cohesion by Michael-type addition, the adhesion and cohesion of this bioadhesive could be balanced by varying the relative concentrations of C-CC and E-CC. In another example, Ryu et al., developed a tissue bioadhesive by crosslinking catechol-conjugated chitosan (CHI-C) with terminally thiolated Pluronic F-127 triblock copolymer (Plu-SH) (Fig. 4) [35]. At higher pH (above neutral), catechol becomes *o*-quinone which can undergo Michael-type addition with thiol. CHI-C/Plu-SH

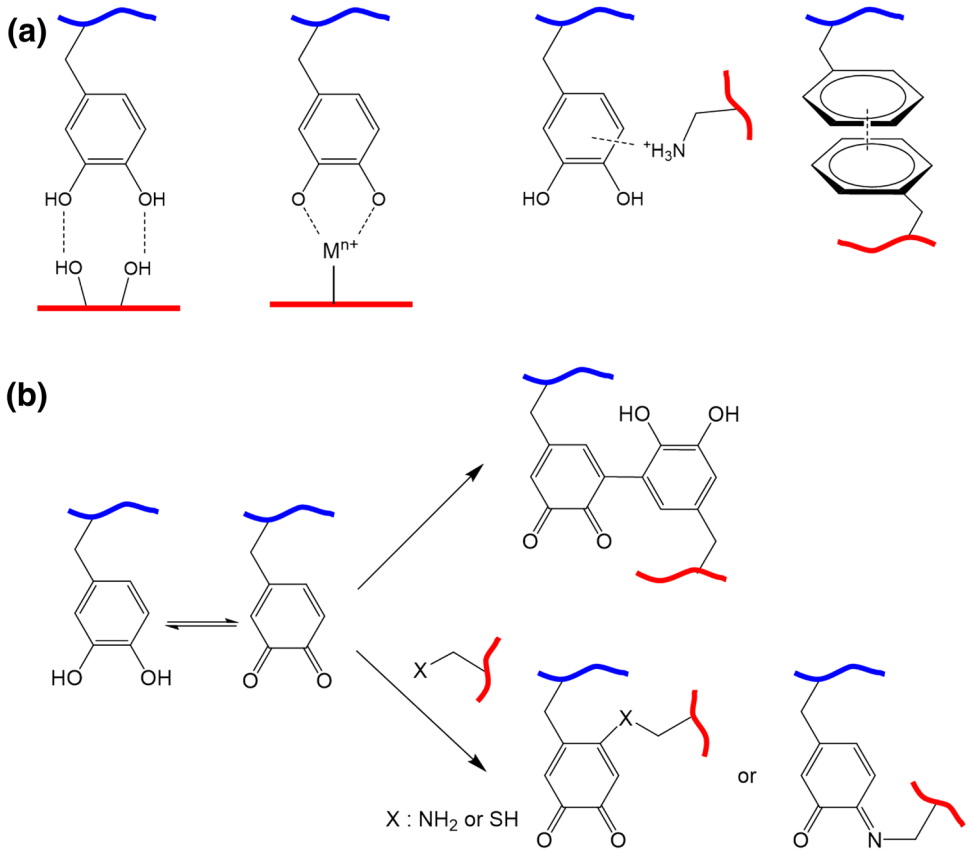


Fig. 3 **a** Physical interaction and **b** chemical reaction pathways of catechol-based polymers for enhancing cohesion and adhesion

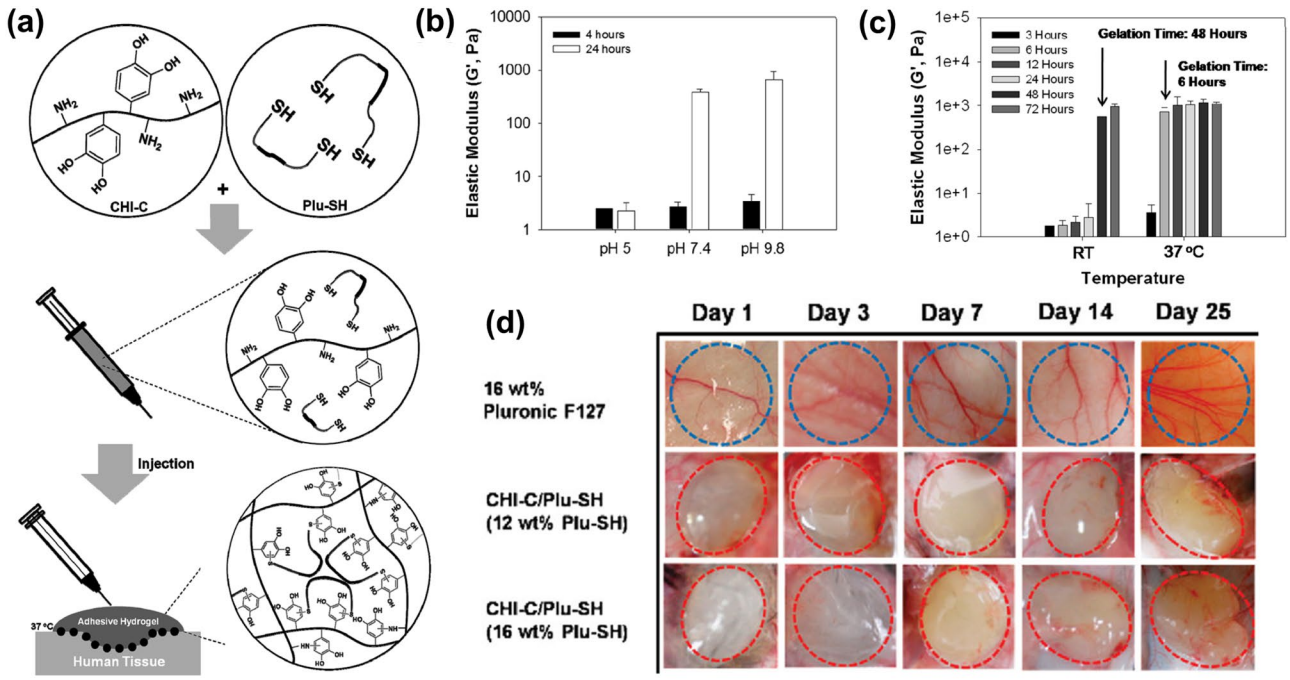


Fig. 4 **a** Schematic illustration of an injectable hydrogel bioadhesive by crosslinking catechol-conjugated chitosan (CHI-C) with terminally thiolated Pluronic F-127 triblock copolymer (Plu-SH). **b**, **c** Mechanical properties of CHI-C/Plu-SH hydrogel at different pH's and temperatures measured at different times. (d) In vivo evaluation of tissue-injected CHI-C/Plu-SH hydrogel. The amount of remaining hydrogel after was monitored. Reproduced with permission from Ref.[35]. Copyright © 2011 American Chemical Society

mixture remains a viscous solution at room temperature, but it becomes a stronger hydrogel at higher temperature of 37 °C, caused by the thermoresponsive gelling behavior of Pluronic F-127. This thermoresponsive physical crosslinking characteristic allowed the CHI-C/Plu-SH hydrogel to be used as a tissue-injectable bioadhesive. The adhesive hydrogel CHI-C/Plu-SH showed strong adhesiveness to soft tissue and mucous layers and demonstrated superior hemostatic properties.

Lih et al. developed a chitosan grafted with PEG-tyramine (CPT), which can be enzymatically crosslinked by horseradish peroxidase in the presence of H_2O_2. The CPT hydrogels exhibited 3 to 20 times the adhesive strength of a commercial fibrin glue (Greenplast®) by using different concentrations of H_2O_2. It also promoted wound healing and reduced fibrosis demonstrated using an in vivo skin incision model [36]. Li et al. similarly fabricated an injectable chitosan hydrogel bioadhesive consisting of two chitosans modified with tetrazine and trans-cyclooctene [37]. By taking advantage of fast and specific inverse-demand Diels–Alder cycloaddition reaction, a series of bioadhesive were prepared by employing copper-free click chemistry. In addition, the adhesive strength increased 2.3 times higher than that of the conventional fibrin glue when 4-arm PEG aldehyde was used as a crosslinking agent.

The ability of catechol to undergo metal coordination has also been a key mechanism to enhance adhesion. Wang et al. developed a double-crosslinking double network hydrogel by simultaneously introducing two types of crosslinking mechanisms to chitosan; photo-initiated radical crosslinking by methacrylic functionalization and Fe^{3+} coordination by catechol [38]. The improved mechanical strength as well as additional adhesion sites provided by catechol also greatly improved the adhesive strength.

Cellulose is the most abundant biopolymer on earth, as the major structural component of plants as well as microbial species [39]. Due to the high mechanical strength owing to the fibrous nature, assembled by hydrogen bonding between β-D-glucopyranose units, in addition to the abundant and inexpensive source, cellulose is one of the most important industrial materials such as textile, paper, and construction. Traditionally in biomedicine, cellulose is mostly used as wound dressing in the form of woven fabric. More recently, bacterial cellulose (BC), which can be produced in industrial scale via bacterial fermentation, is increasingly utilized over plant-derived cellulose. BC has more scalable and superior mechanical properties due to higher degree of crystallinity (devoid of nonfibrous components) and three dimensional nanofibrous network, which give rise to higher mechanical strength and larger surface area [40]. Larger fibrous cellulose can be processed into smaller cellulose nanofibrils (or nanocrystals) that are dispersible in aqueous media and used as fillers for composite materials [41]. Chemically modified cellulose to impart aqueous solubility, such as carboxymethylcellulose (CMC), has long been used in drug delivery and tissue engineering applications. CMC has a long history in adhesive technology, as CMC is the major component of the majority of commercial denture adhesives (e.g. Fixodent®, SeaBond®, Super Polygrip®) [42]. A blended solution consisting of CMC and other polymers show highly variable viscoelastic properties that provide adequate amount of adhesion while easily be detached by force, which is a prerequisite characteristic for denture adhesive. CMC-based hydrogel has been used as tissue adhesives for as carriers for drugs and drug delivery system, superabsorbent material or tissue adhesives.

Like other polysaccharides, cellulose is also heavily investigated for bioadhesive applications. In order to control the cohesion and adhesion, cellulose is similarly modified with reactive functional groups, such as catechol. Khamrai et al. have prepared a composite bioadhesive consisting of reduced graphene (rGO) and silver nanoparticles (Ag NP) with catechol (DOPA)-modified BC (BC-DOPA) (Fig. 5) [43]. The presence of rGO and Ag NP's within BC-DOPA bioadhesive significantly increased the mechanical strength, while Ag NP's also imparted anti-bacterial effect against both Gram-positive and Gram-negative bacteria. Alternatively, dispersible cellulose nanocrystals can be incorporated into a polymeric network as a filler to generate nanocomposite structure. Li et al. developed a nanocomposite bioadhesive by incorporating cellulose nanocrystals mineralized with calcium carbonate into catechol- and vanillin-modified polylysine [44]. The nanocomposite bioadhesive demonstrated significant improvement in both mechanical and adhesion strengths over the polymer-only adhesive.

Due to their inherent fibrous nature, cellulose has been long used to generate nanofibers for various biomedical applications. Nanofibers have high porosity and surface area, as compared to other monolithic structures such as hydrogels and elastomers, thereby having greater degrees of interaction with biological molecules. Taking advantage of these attributes, cellulose nanofibers are also being used as bioadhesives. For example, Kim et al. developed BC nanofiber conjugated with the antibody for involucrin, a membrane protein commonly found in skin [45]. The antigen–antibody interaction allowed the BC nanofiber to form strong adhesion to the skin.

3 Protein-based bioadhesives

Proteins are also widely explored as bioadhesives [14]. Generally, polysaccharides can be obtained in large quantities from inexpensive source than proteins that are more expensive and difficult to extract in large quantities. But proteins are highly multifunctional in nature due to different amino

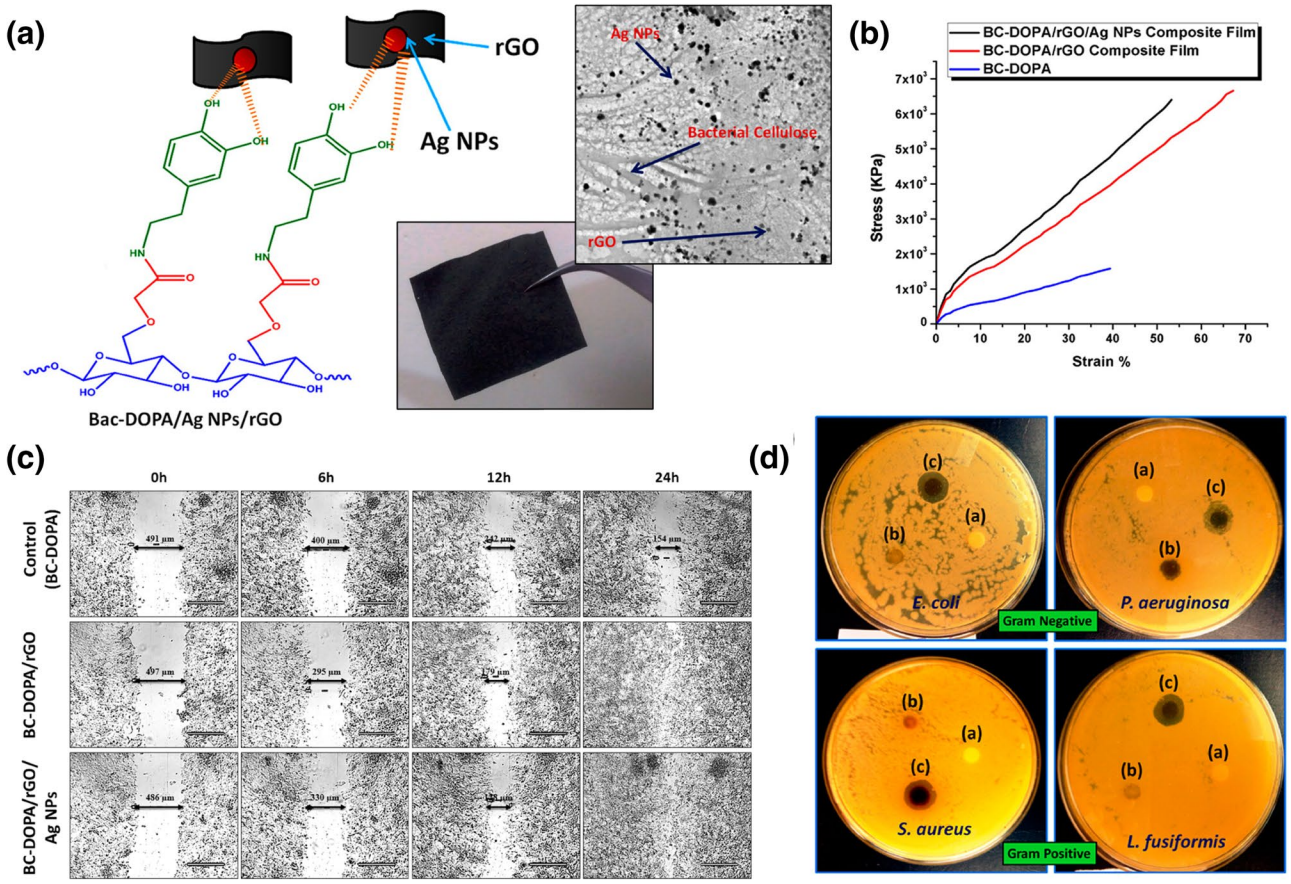


Fig. 5 **a** Schematic illustration, photograph and TEM image of composite bioadhesive consisting of silver nanoparticles (Ag NPs) and reduced graphene oxide (rGO) in catechol-modified bacterial cellulose (Bac-DOPA). **b** mechanical strength, **c** cell proliferation, and **d** antibacterial effect of Bac-DOPA/AgNPs/rGO were all greater than those of Bac-DOPA. Reproduced with permission from Ref.[43]. Copyright © 2019 American Chemical Society

acid compositions, which can be manipulated to present various functional groups used for crosslinking in addition to innate physical crosslinking via hydrogel bonding and hydrophobic interaction [46]. In addition, unmodified proteins can also have the ability to be crosslinked enzymatically, such as transglutaminase and horseradish peroxidase. Furthermore, proteins are highly biodegradable due to proteinases inherent in our bodies, which makes them ideally suited for implantable applications.

One of the first type of protein-based bioadhesive to be approved for medical use was fibrin hydrogel (e.g. TISSEEL® and EVICEL®) as a surgical sealant, taking advantage of the natural blood coagulation mechanism by which fibrinogen polymerization mediated by thrombin in the presence of Ca^{2+} and Factor XIII leads to clot formation that seals the wound. Since all the components are naturally derived without any chemical modifications, the fibrin hydrogel is highly biocompatible and biodegradable. For the same reason, however, it is readily bioresorbable, which could limit long-term applications with critically diminishing mechanical strength. There is a potential risk of immune response arising from the source of protein and the infection. Also, being composed of expensive proteins, it is quite costly and must be stored at low temperature.

Since fibrin hydrogel is formed by enzymatic crosslinking of native proteins, chemical modification of fibrin is not generally feasible, as it may lead to unwanted change in the crosslinking process [47]. In order to improve the cohesive and adhesive properties of fibrin hydrogels, introducing a secondary polymeric network or nanocomposite has been explored. For example, Sundaram et al. developed a fibrin nanocomposite hydrogel laden with chitin and tigecycline-loaded gelatin nanoparticles (tGNPs) (Fig. 6) [48]. While chitin acted as a secondary network for semi-IPN structure, tGNPs acted as nanofillers within the chitin-fibrin network. The presence of both chitin and tGNPs substantially increased the mechanical properties, up to 280-fold increase in elastic modulus from the pure fibrin hydrogel. While the adhesion strengths measured from lap-shear tests were similar, those measured from burst pressure tests were

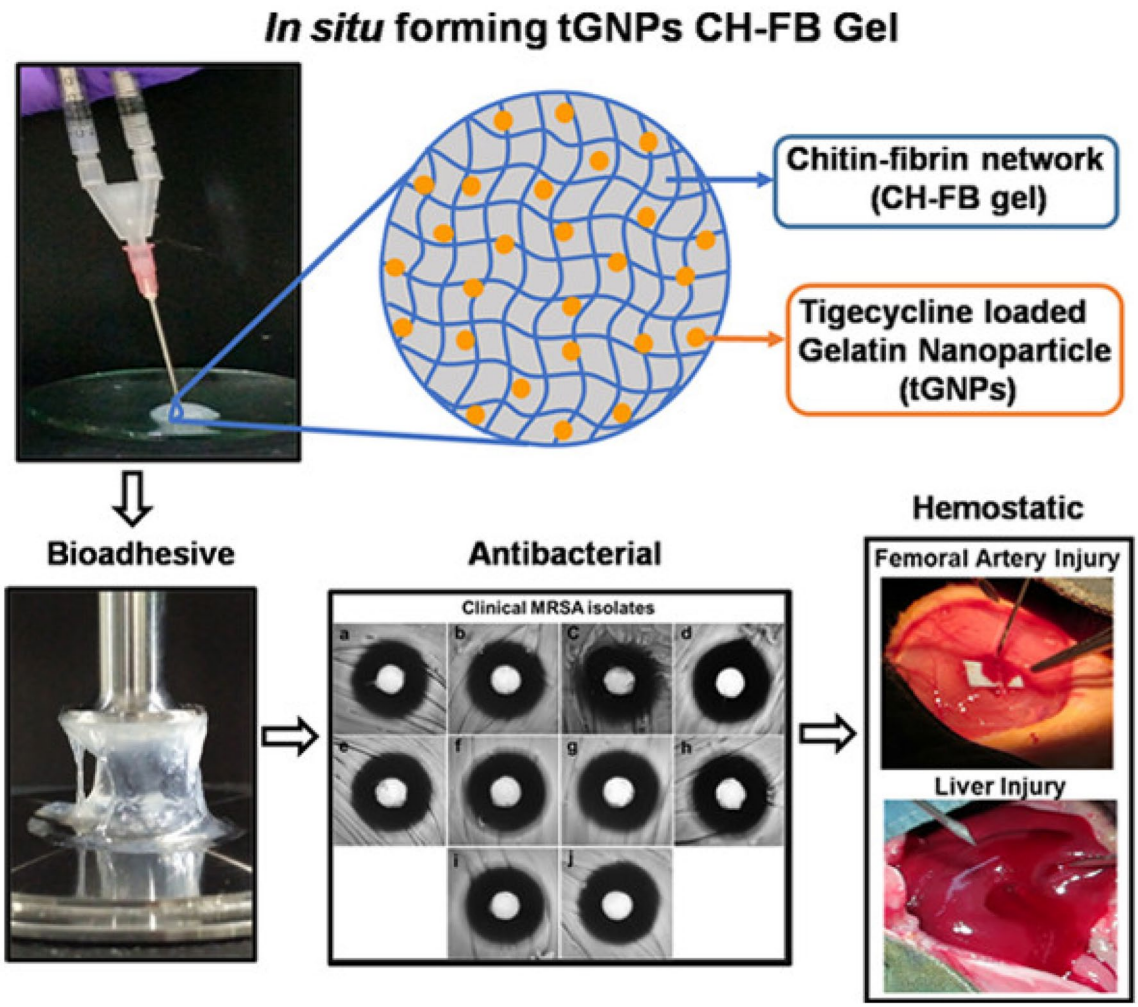


Fig. 6 Nanocomposite hydrogel bioadhesive with improved adhesive strength and antibacterial property was generated by encapsulating tigecycline-loaded gelatin nanoparticles (tGNPs) into chitin-fibrin hydrogel. Reproduced with permission from ref.[48]. Copyright © 2018 American Chemical Society

significantly enhanced by the presence of chitin and tGNPs, indicating that the enhanced cohesion could prevent mechanical failure of the bioadhesive. Furthermore, encapsulation of tigecycline, an antibiotic, into the chitin-fibrin hydrogel demonstrated antibacterial effect. Zhang et al. developed an IPN network hydrogel consisting of hyaluronic acid and fibrin [49]. Hyaluronic acid was modified to present thiol groups, so that it can form hyaluronic acid network by disulfide bond. The IPN hydrogel demonstrated higher mechanical strength and slower biodegradation.

Gelatin has long been a fixture in food and drug development as a gelling material, as it undergoes temperature-induced sol–gel transition. It is obtained mostly from by partial hydrolysis of collagen in animal tissues (e.g. porcine and bovine skin). In addition to natural gelation, biocompatibility, bioactivity (cell adhesion and biodegradation), and relatively abundant source compared to other proteins have made gelatin one of the most widely used biopolymer for biomedical applications mainly for developing drug delivery systems and tissue engineering scaffolds [50, 51]. More recently, chemical modification of gelatin to present methacrylate, often termed gelatin methacrylate ('GelMA') has gained significant popularity for developing photocrosslinkable gelatin hydrogel [52]. Naturally, GelMA hydrogels have also been broadly investigated as bioadhesives. For example, Assmann et al. explored the photocrosslinked GelMA hydrogel as a bioadhesive for tissue adhesion [53]. The adhesion strength was controlled by the concentration of GelMA and the UV dosage for photocrosslinking. Using in vivo lung leakage model, the GelMA hydrogel was shown to effectively seal the leakage.

The adhesive properties of GelMA hydrogels could be controlled by incorporating additional polymeric components. For example, Zhao et al. also developed a

photocrosslinkable GelMA hydrogel as a bioadhesive supplemented with oxidized dextran presenting aldehyde groups (ODex) (Fig. 7) [54]. ODex could be crosslinked with both GelMA and biological tissue via Schiff base formation. The mechanical stiffness could be controlled in a wide range, up to 400 kPa with GelMA and ODex concentrations, while the adhesive strength also increased concurrently. This proved that the increase in cohesion within this range did not compromise and rather augmented the adhesion. Similarly, Tavafoghi et al. developed a hybridized GelMA and alginate methacrylate (AlgMA) hydrogel bioadhesive [55]. The presence of methacrylate on both gelatin and alginate allowed copolymerization by photocrosslinking. Additionally, the ability of alginate to undergo ionic crosslinking with divalent ions also afforded enhancing the mechanical strength.

Like other biopolymers, gelatin has also been modified with catechol groups to enhance the adhesion strength of gelatin bioadhesive. Liu et al. prepared catechol- (Gel-Ca) and phenol-modified (Gel-Ph) gelatin bioadhesives [56]. Both Gel-Ph and Gel-Ca hydrogels could be prepared by photocrosslinking of phenolic groups (PPG and PCG, respectively), while Gel-Ca hydrogel could also be prepared by ionic crosslinking with Fe^{3+} (ICG). It was shown that the adhesive strengths of PPG and PCG were much higher than that of ICG. Also, the rate of biodegradation was much faster for ICG. These results indicated that photocrosslinking was more effective in controlling the cohesion and adhesion. Regardless of the mode of crosslinking, they all demonstrated low cytotoxicity.

4 Polyphenol-based bioadhesives

Polyphenols refer to a large family of structurally diverse organic compounds mostly found in plants that contain multiple phenolic groups, such as phenolic acids, flavonoids, coumarins, and tannins [57]. Their biological roles include pigment formation and protection against harmful radiation and pathogens. With the recent rise in popularity of catechol as a mediator of adhesion, polyphenols are being viewed as

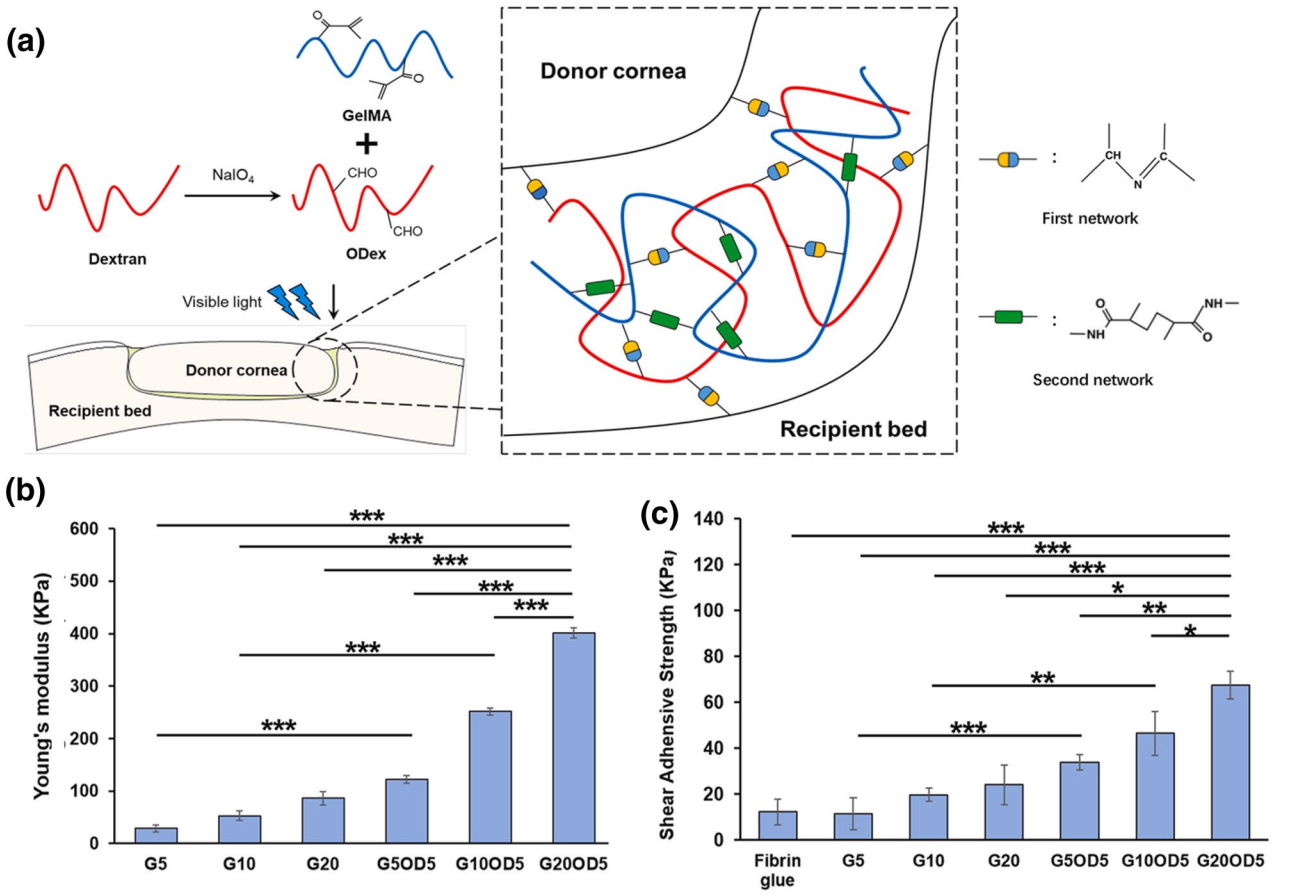


Fig. 7 **a** Schematic illustration of GelMA-ODex bioadhesive for suture-less keratoplasty. ODex is crosslinked with both GelMA and the biological tissue (cornea and recipient bed), and GelMA is photocrosslinked to form hydrogel. **b** Young's moduli and **c** shear adhesive strengths of GelMA-ODex bioadhesives controlled with the polymer concentrations. Reproduced with permission from Ref. [54]. under Creative Commons and Attribution license (CC BY-NC-ND 4.0)

a viable alternative to catechol-presenting polymers for bioadhesives, as they naturally contain phenolic units and could be economically obtained from large-scale production [58]. Polyphenols can be mass-produced in an eco-friendly manner by extraction of agricultural and forestial byproducts. Due to antioxidant properties, polyphenols also display antimicrobial properties. Polyphenol-based bioadhesives cured by physical association have been shown to demonstrate self-healing properties.

Tannins are a class of branched macromolecules consisting of phenolic groups such as gallol and catechol units. Their exact structures and sizes vary widely depending on the biological sources. The oligomeric and polymeric tannic acid (TA), consisting of gallic ester units, are deemed especially attractive and widely explored as bioadhesive, because they are water soluble and can undergo cohesive interactions due to the phenolic units forming larger and mechanically robust network structures such as hydrogels. [59]

The phenolic groups on TA are capable of various physical interactions as hydrogen bond, hydrophobic interaction, and ionic interaction, which allows TA to hybridize strongly with a diverse array of polymers, without the need for additional chemical reaction schemes. Shin et al. utilized this capability of TA by developing TA-DNA (TNA) hydrogel, in which TA acted as a "molecular glue" to hold DNA molecules together [60]. Since DNA consists of a series of heterocyclic aromatic base, it could bind strongly with TA via both hydrophobic interaction and hydrogen bonding. TNA hydrogel demonstrated several advantageous qualities, such as biodegradability (ester groups in TA) and hemostatic properties (phosphate groups in DNA), in addition to adhesive properties. Luo et al. developed a hydrogel bioadhesive by crosslinking TA with silk fibroin (SF) [61]. SF is a protein with extensive hydrophobic residues capable of forming hydrogen bonds and hydrophobic interactions. Therefore, it can also undergo substantial intermolecular interactions with TA by the same mechanism, resulting in enhanced mechanical toughness. Ke et al. further engineered TA-SF hydrogel bioadhesive to enhance the antimicrobial properties by the addition of Ag NP's. [62]

TA can also interact with synthetic polymers that possess functional moieties capable of physical interactions. Fan et al. prepared a hydrogel adhesive composed of poly(dimethyl diallyl ammonium chloride) (PDDA) and TA in the presence of Fe^{3+} via ionic interaction (Fig. 8a) [63]. TA could interact with cationic PDDA via electrostatic interaction, while also forming coordination with Fe^{3+} at lower pH, resulting in strong cohesion. The crosslinking density of the PDDA-TA hydrogel was controlled by the PDDA/TA ratio. Furthermore, the adhesion strength was well maintained at lower pH due to the increasing amount of hydrogen bonds. Fan et al. developed a nanocomposite hydrogel as a hemostatic adhesive by incorporating kaolin, aluminum silicate mineral, into TA-polyacrylamide (PAAm) hydrogel [64]. TA can participate in the radical polymerization of acrylamide to form PAAm through the radicals generated on the gallol groups to form hydrogels. The mechanical toughness of TA-PAAm hydrogel was significantly enhanced by incorporating kaolin as a filler. Wen et al. improved the mechanical toughness of polyethylene glycol polyurethane (PEG-PU) hydrogel by incorporating TA (Fig. 8b) [65]. PEG-PU hydrogel was first prepared by crosslinking PEG-PU prepolymer with trimethylolpropane as a crosslinker. TA was incorporated into the PEG-PU network in order to induce physical crosslinking with PEG-PU via hydrogen bonding to urethane groups. The resulting TA-PU hydrogel demonstrated significant increases in both mechanical toughness and adhesion strength.

Owing to its ability to adhere a wide range of proteins via physical interaction, TA can also be used for hemostatic applications. Kim et al. produced a simple and highly scalable hemostatic bioadhesive by mixing TA with PEG ('TAPE') [66]. The intermolecular hydrogen bonding between TA and PEG was strong enough that the adhesion strength of TAPE was 250% higher than a commercial fibrin adhesive. Jin et al. developed cholesteryl liquid crystal emulsion (CLCE) modified with TA [67]. The presence of TA induced and facilitated blood coagulation, while the change in optical properties of CLCE during the coagulation could be used as the color indicator.

The phenolic groups on TA are also capable of various chemical reactions. For example, taking advantage of catechol and gallol to become quinone by oxidation, Hao et al. employed a TA-sliver dual catalysis strategy based on a reversible redox reaction, in which catechol groups on TA reduced Ag^{+} to Ag NP's while being oxidized to quinone and semiquinone, which in turn rapidly initiated the radical polymerization to generate PAAm-cellulose nanocrystal (CNC) hydrogel [68]. Incorporating CNC, along with the presence of TA providing additional physical association, showed marked increased in mechanical properties. In addition, the newly formed Ag NP's imparted antimicrobial properties. In another example of utilizing oxidized TA, Guo et al. developed a TA-gelatin hydrogel adhesive by reacting oxidized TA with gelatin [69]. At higher pH with high oxygen concentration, phenolic groups of TA underwent oxidation to form quinone, which could react with amine groups of gelatin via Michael addition.

With the recent rise in popularity of wearable biosensors, biopolymers are increasingly investigated as a sensor platform for their biocompatibility and mechanical conformability and adhesive properties. TA is an excellent candidate for this purpose for its natural adhesive properties and the physical interaction with other materials for added functionalities. Qiao et al. developed a composite hydrogel system consisting of sodium alginate, TA and crosslinked

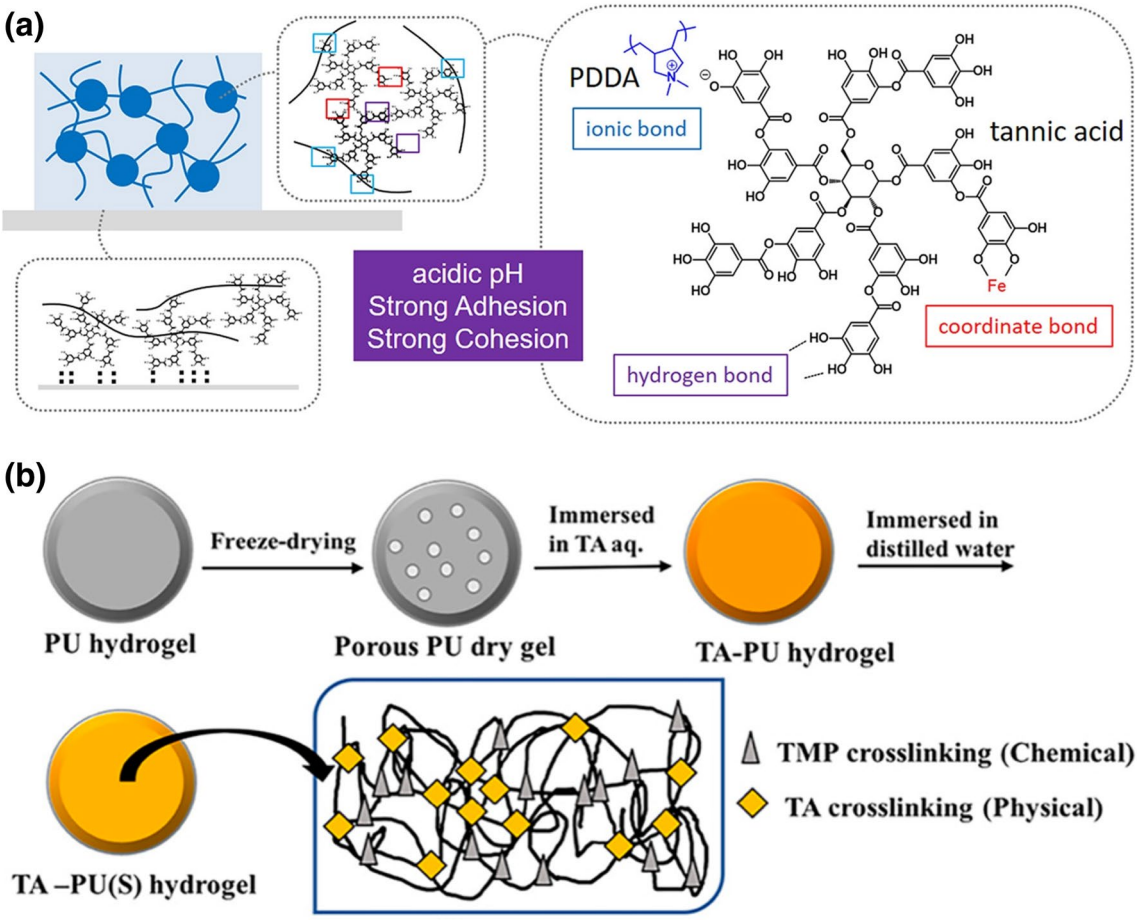


Fig. 8 **a** The hydrogel bioadhesive consisting of poly(dimethyl diallyl ammonium chloride) (PDDA) and tannic acid (TA) in the presence of Fe^{3+}. Increased Fe-catechol coordination and hydrogen bonding at lower pH contributed to both adhesion and cohesion of the hydrogel. Reproduced with permission from Ref. [63]. Copyright © 2017 American Chemical Society. **b** The mechanical strength of polyurethane (PU) hydrogel adhesive was enhanced by incorporating TA. PU hydrogel was first prepared with TMP crosslinker, followed by infusing TA into the dried PU mesh. Reproduced with permission from Ref. [65]. under Creative Commons and Attribution license (CC BY 4.0)

polyacrylamide ('STP hydrogel') (Fig. 9) [70]. This hybridized material demonstrated improved mechanical stretchability, self-healing, adhesiveness and ionic conductivity. The STP hydrogel attached on skin could detect various bodily movement by measuring the change in resistance in response to mechanical strain.

5 Conclusions and future perspectives

Adhesives are one of the most ubiquitous materials used today, from household glues to high-strength industrial adhesives. With the increasing awareness of environment and human health, extensive research efforts have been made to develop biocompatible and eco-friendly adhesives by using materials and employing crosslinking schemes that are less toxic and eco-friendly. For this purpose, the obvious choice of material has been biopolymers that can be obtained from scalable industrial production, most notably cellulose, natural rubber, lignin and alginate.

The concept of "bioadhesive", in its truest sense, was originated mainly for wound closure. Bioadhesive can seal the wound gap that is generally not possible for sutures and tapes to prevent the leakage of biological fluids and prevent infection while the tissue regeneration takes place. Bioadhesive can also act as a drug delivery system to further assist and facilitate the regenerative process. The original bioadhesive developed for wound closure was cyanoacrylate, which is still widely being used today. It has the advantage of rapid-curing rate, high mechanical and adhesion strengths, but it is also shown to elicit variable inflammatory responses, especially if it entered the wound gap. Therefore, the current bioadhesive research for wound closure is mainly focused on improving the

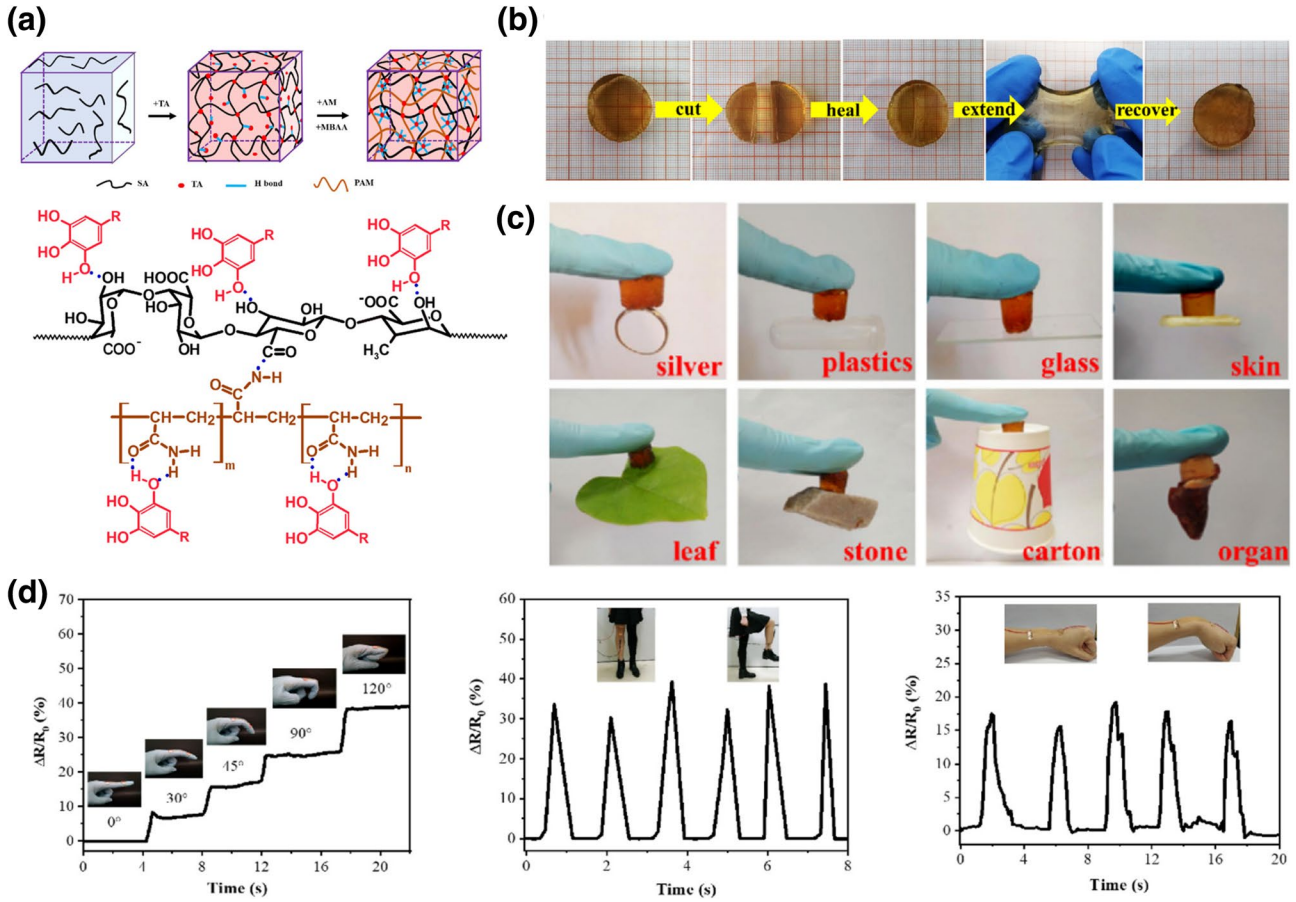


Fig. 9 **a** STP hydrogel consisting of sodium alginate (SA) TA, and polyacrylamide (PAM). STP hydrogel demonstrated **b** self-healing and **c** adhesion towards various substrates. **d** The change in resistance (R/R_0) of STP hydrogel attached to different body parts via various movements. Reproduced with permission from Ref. [70]. Copyright © 2019 American Chemical Society

biocompatibility while not critically jeopardizing the cohesion and adhesion strengths. This aspect has become more vital as the biocompatibility requirement for bioadhesive is becoming stringent, especially for internal surgical sealant. This was the main reason for the recent development and popularity of natural fibrin hydrogel-based bioadhesive (e.g. TISSEEL®). However, it still remains a challenge to meet all the criteria required for surgical adhesives to be more broadly applicable; biocompatibility, strong and controllable adhesion strength, timely curing rate and degradation, and cost-effectiveness.

In addition to surgical applications, the recent rise in wearable biomedical devices is also driving the bioadhesive technology [71]. Wearable devices as biosensors, drug delivery systems and engineered tissues come in all shapes and sizes, and are made using a wide variety of materials. Also, there are clear operational differences, such mode of delivery (internal vs. topical) and duration (temporary vs. permanent). These factors all call for bioadhesives with tailor-made properties.

Acknowledgements This study was supported by the 2022 Research Fund (1.220130.01) of UNIST (Ulsan National Institute of Science and Technology), Mid-Career Researcher Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (2022R1A2C2009174), and Technology Innovation Program (or Industrial Strategic Technology Development Program) (20009198, Development and demonstration of biodegradable bioplastic prototype) funded by the Ministry of Trade, Industry and Energy (MOTIE, Korea).

References

1. M. Mehdizadeh, J. Yang, Design strategies and applications of tissue bioadhesives. Macromol. Biosci. **13**, 271–288 (2013)
2. C.-M. Lehr, J. Haas, Developments in the area of bioadhesive drug delivery systems. Expert Opin. Biol. Ther. **2**, 287–298 (2002)
3. J. Park, Y. Kim, B. Chun, J. Seo, Rational engineering and applications of functional bioadhesives in biomedical engineering. Biotechnol. J. **16**, 2100231 (2021)
4. S. Nam, D. Mooney, Polymeric tissue adhesives. Chem. Rev. **121**, 11336–11384 (2021)

5. G.M. Taboada, K. Yang, M.J.N. Pereira, S.S. Liu, Y. Hu, J.M. Karp, N. Artzi, Y. Lee, Overcoming the translational barriers of tissue adhesives. Nat. Rev. Mater. **5**, 310–329 (2020)
6. S.J. Marshall, S.C. Bayne, R. Baier, A.P. Tomsia, G.W. Marshall, A review of adhesion science. Dent. Mater. **26**, e11–e16 (2010)
7. S. Khanlari, M.A. Dubé, Bioadhesives: a review. Macromol. React. Eng. **7**, 573–587 (2013)
8. M.D. Brigham, A. Bick, E. Lo, A. Bendali, J.A. Burdick, A. Khademhosseini, Mechanically robust and bioadhesive collagen and photocrosslinkable hyaluronic acid semi-interpenetrating networks. Tissue Eng. Part A **15**, 1645–1653 (2009)
9. Y. Zhang, Q. Chen, Z. Dai, Y. Dai, F. Xia, X. Zhang, Nanocomposite adhesive hydrogels: from design to application. J. Mater. Chem. B **9**, 585–593 (2021)
10. C. Fang, Z. Lin, Effect of propyleneimine external cross-linker on the properties of acrylate latex pressure sensitive adhesives. Int. J. Adhes. Adhes. **61**, 1–7 (2015)
11. D.E. Discher, D.J. Mooney, P.W. Zandstra, Growth factors, matrices, and forces combine and control stem cells. Science **324**, 1673–1677 (2009)
12. G. Trujillo-de Santiago, R. Sharifi, K. Yue, E.S. Sani, S.S. Kashaf, M.M. Alvarez, J. Leijten, A. Khademhosseini, R. Dana, N. Annabi, Ocular adhesives: design, chemistry, crosslinking mechanisms, and applications. Biomaterials **197**, 345–367 (2019)
13. Y. Bu, A. Pandit, Cohesion mechanisms for bioadhesives. Bioact. Mater. **13**, 105–118 (2022)
14. S. Rathi, R. Saka, A.J. Domb, W. Khan, Protein-based bioadhesives and bioglues. Polym. Adv. Technol. **30**, 217–234 (2019)
15. N. Wanasingha, N.K. Dutta, N.R. Choudhury, Emerging bioadhesives: from traditional bioactive and bioinert to a new biomimetic protein-based approach. Adv. Colloid Interface Sci. **296**, 102521 (2021)
16. Y. Wen, J.K. Oh, Recent strategies to develop polysaccharide-based nanomaterials for biomedical applications. Macromol. Rapid Commun. **35**, 1819–1832 (2014)
17. H. Hu, F.-J. Xu, Rational design and latest advances of polysaccharide-based hydrogels for wound healing. Biomater. Sci. **8**, 2084–2101 (2020)
18. E. Twizeyimana, S. Zhang, J.F. Mukerabigwi, Z. Ge, Oxidized alginate hydrogel-based derivatives with optimized features for cell culture scaffold. Macromol. Res. **30**, 238–244 (2022)
19. H. Li, R. Niu, J. Yang, J. Nie, D. Yang, Photocrosslinkable tissue adhesive based on dextran. Carbohydr. Polym. **86**, 1578–1585 (2011)
20. T. Wang, J. Nie, D. Yang, Dextran and gelatin based photocrosslinkable tissue adhesive. Carbohydr. Polym. **90**, 1428–1436 (2012)
21. N. Oliva, S. Shitreet, E. Abraham, B. Stanley, E.R. Edelman, N. Artzi, Natural tissue microenvironmental conditions modulate adhesive material performance. Langmuir **28**, 15402–15409 (2012)
22. M.C. Giano, Z. Ibrahim, S.H. Medina, K.A. Sarhane, J.M. Christensen, Y. Yamada, G. Brandacher, J.P. Schneider, Injectable bioadhesive hydrogels with innate antibacterial properties. Nat. Commun. **5**, 4095 (2014)
23. M.N.V. Ravi Kumar, A review of chitin and chitosan applications. React. Funct. Polym. **46**, 1–27 (2000)
24. M. Rinaudo, Chitin and chitosan: properties and applications. Prog. Polym. Sci. **31**, 603–632 (2006)
25. N. Mati-Baouche, P.-H. Elchinger, H. de Baynast, G. Pierre, C. Delattre, P. Michaud, Chitosan as an adhesive. Eur. Polym. J. **60**, 198–212 (2014)
26. M. Kim, Y. Ahn, K. Lee, W. Jung, C. Cha, In situ facile-forming chitosan hydrogels with tunable physicomechanical and tissue adhesive properties by polymer graft architecture. Carbohydr. Polym. **229**, 115538 (2020)
27. T.M. Ways, W. Lau, V. Khutoryanskiy, Chitosan and its derivatives for application in mucoadhesive drug delivery systems. Polymers **10**, 267 (2018)
28. Z. Sang, J. Qian, J. Han, X. Deng, J. Shen, G. Li, Y. Xie, Comparison of three water-soluble polyphosphate tripolyphosphate, phytic acid, and sodium hexametaphosphate as crosslinking agents in chitosan nanoparticle formulation. Carbohydr. Polym. **230**, 115577 (2020)
29. J.S.L. Tan, C. Roberts, N. Billa, Pharmacokinetics and tissue distribution of an orally administered mucoadhesive chitosan-coated amphotericin B-loaded nanostructured lipid carrier (NLC) in rats. J. Biomater. Sci. Polym. Ed. **31**, 141–154 (2020)
30. L.T. Hao, S. Park, S. Choy, Y.-M. Kim, S.-W. Lee, Y.S. Ok, J.M. Koo, S.Y. Hwang, D.S. Hwang, J. Park et al., Strong, multifaceted guanidinium-based adhesion of bioorganic nanoparticles to wet biological tissue. JACS Au **1**, 1399–1411 (2021)
31. D.H. Oh, P.L. Thi, K.D. Park, A comparative study of enzyme-mediated crosslinking of catechol- and phenol-functionalized tetronic hydrogels. Macromol. Res. **30**, 190–197 (2022)
32. H. Lee, S.M. Dellatore, W.M. Miller, P.B. Messersmith, Mussel-inspired surface chemistry for multifunctional coatings. Science **318**, 426–430 (2007)
33. W. Zhang, R. Wang, Z. Sun, X. Zhu, Q. Zhao, T. Zhang, A. Cholewinski, F. Yang, B. Zhao, R. Pinnaratip et al., Catechol-functionalized hydrogels: biomimetic design, adhesion mechanism, and biomedical applications. Chem. Soc. Rev. **49**, 433–464 (2020)
34. M.K. Park, M.-X. Li, I. Yeo, J. Jung, B.-I.L. Yoon, Y.K. Joung, Balanced adhesion and cohesion of chitosan matrices by conjugation and oxidation of catechol for high-performance surgical adhesives. Carbohydr. Polym. **248**, 116760 (2020)
35. J.H. Ryu, Y. Lee, W.H. Kong, T.G. Kim, T.G. Park, H. Lee, Catechol-functionalized chitosan/pluronic hydrogels for tissue adhesives and hemostatic materials. Biomacromol **12**, 2653–2659 (2011)
36. E. Lih, J.S. Lee, K.M. Park, K.D. Park, Rapidly curable chitosan–PEG hydrogels as tissue adhesives for hemostasis and wound healing. Acta Biomater. **8**, 3261–3269 (2012)
37. S. Li, J. Zhou, Y. Huang, J. Roy, N. Zhou, K. Yum, X. Sun, L. Tang, Injectable click chemistry-based bioadhesives for accelerated wound closure. Acta Biomater. **110**, 95–104 (2020)
38. L. Wang, X. Zhang, K. Yang, Y.V. Fu, T. Xu, S. Li, D. Zhang, L.-N. Wang, C.-S. Lee, A novel double-crosslinking-double-network design for injectable hydrogels with enhanced tissue adhesion and antibacterial capability for wound treatment. Adv. Funct. Mater. **30**, 1904156 (2020)
39. H. Seddiqi, E. Oliaei, H. Honarkar, J. Jin, L.C. Geonzon, R.G. Bacabac, J. Klein-Nulend, Cellulose and its derivatives: towards biomedical applications. Cellulose **28**, 1893–1931 (2021)
40. C. Zhong, Industrial-Scale production and applications of bacterial cellulose. Front. Bioeng. Biotechnol. **8**, 605374 (2020)
41. Z.X. Ting, L.J. Yan, Effects of bacterial cellulose whisker melting composite on crystallization and mechanical properties of PHBV composites. Macromol. Res. **30**, 325–333 (2022)
42. D.R. Kore, M.T. Kattadiyil, D.B. Hall, K. Bahjri, In vitro comparison of the tensile bond strength of denture adhesives on denture bases. J. Prosthet. Dent. **110**, 488–493 (2013)
43. M. Khamrai, S.L. Banerjee, S. Paul, A.K. Ghosh, P. Sarkar, P.P. Kundu, A mussel mimetic, bioadhesive, antimicrobial patch based on dopamine-modified bacterial cellulose/rGO/Ag NPs: a green approach toward wound-healing applications. ACS Sustain. Chem. Eng. **7**, 12083–12097 (2019)
44. K. Li, S. Jin, F. Zhang, Y. Zhou, G. Zeng, J. Li, S.Q. Shi, J. Li, Bioinspired phenol-amine chemistry for developing bioadhesives based on biomineralized cellulose nanocrystals. Carbohydr. Polym. **296**, 119892 (2022)

45. S. Kim, J. Ko, J.H. Choi, J.Y. Kang, C. Lim, M. Shin, D.W. Lee, J.W. Kim, Antigen-antibody interaction-derived bioadhesion of bacterial cellulose nanofibers to promote topical wound healing. Adv. Funct. Mater. **32**, 2110557 (2022)
46. A. Totosaus, J.G. Montejano, J.A. Salazar, I. Guerrero, A review of physical and chemical protein-gel induction. Int. J. Food Sci. Technol. **37**, 589–601 (2002)
47. M.A. Rozenfeld, V.V. Leonova, M.L. Konstantinova, S.D. Razumovskii, Mechanism of enzymatic crosslinking of fibrinogen molecules. Biol. Bull. **35**, 578–584 (2008)
48. M. N. Sundaram, V. Krishnamoorthi Kaliannagounder, V. Selvaprithiviraj, K. Suresh, M. Biswas, R. Vasudevan, A. K. Varma, P.K. Jayakumar, Bioadhesive, hemostatic, and antibacterial in situ chitin–fibrin nanocomposite gel for controlling bleeding and preventing infections at mediastinum.ACS Sustain. Chem. Eng. **6**, 7826–7840 (2018)
49. Y. Zhang, P. Heher, J. Hilborn, H. Redl, D.A. Ossipov, Hyaluronic acid-fibrin interpenetrating double network hydrogel prepared in situ by orthogonal disulfide cross-linking reaction for biomedical applications. Acta Biomater. **38**, 23–32 (2016)
50. K. Su, C. Wang, Recent advances in the use of gelatin in biomedical research. Biotechnol. Lett. **37**, 2139–2145 (2015)
51. H. Jeong, D.Y. Lee, D.H. Yang, Y.-S. Song, Mechanical and cell-adhesive properties of gelatin/polyvinyl alcohol hydrogels and their application in wound dressing. Macromol. Res. **30**, 223–229 (2022)
52. K. Yue, G. Trujillo-de Santiago, M.M. Alvarez, A. Tamayol, N. Annabi, A. Khademhosseini, Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. Biomaterials **73**, 254–271 (2015)
53. A. Assmann, A. Vegh, M. Ghasemi-Rad, S. Bagherifard, G. Cheng, E.S. Sani, G.U. Ruiz-Esparza, I. Noshadi, A.D. Lassaletta, S. Gangadharan et al., A highly adhesive and naturally derived sealant. Biomaterials **140**, 115–127 (2017)
54. X. Zhao, S. Li, X. Du, W. Li, Q. Wang, D. He, J. Yuan, Natural polymer-derived photocurable bioadhesive hydrogels for sutureless keratoplasty. Bioact. Mater. **8**, 196–209 (2022)
55. M. Tavafoghi, A. Sheikhi, R. Tutar, J. Jahangiry, A. Baidya, R. Haghniaz, A. Khademhosseini, Engineering tough, injectable, naturally derived, bioadhesive composite hydrogels. Adv. Healthc. Mater. **9**, 1901722 (2020)
56. Y. Liu, S. Cheong Ng, J. Yu, W.-B. Tsai, Modification and crosslinking of gelatin-based biomaterials as tissue adhesives. Colloids Surf. B. Biointerfaces **174**, 316–323 (2019)
57. A. Shavandi, A.E.-D.A. Bekhit, P. Saeedi, Z. Izadifar, A.A. Bekhit, A. Khademhosseini, Polyphenol uses in biomaterials engineering. Biomaterials **167**, 91–106 (2018)
58. Y.-B. Kwon, S.-R. Lee, T.H. Seo, Y.-K. Kim, Fabrication of a strong artificial nacre based on tannic acid-functionalized graphene oxide and poly(vinyl alcohol) through their multidentate hydrogen bonding. Macromol. Res. **30**, 279–284 (2022)
59. H. Jafari, P. Ghaffari-Bohlouli, S.V. Niknezhad, A. Abedi, Z. Izadifar, R. Mohammadinejad, R.S. Varma, A. Shavandi, Tannic acid: a versatile polyphenol for design of biomedical hydrogels. J. Mater. Chem. B **10**, 5873–5912 (2022)
60. M. Shin, J.H. Ryu, J.P. Park, K. Kim, J.W. Yang, H. Lee, DNA/tannic acid hybrid gel exhibiting biodegradability, extensibility, tissue adhesiveness, and hemostatic ability. Adv. Funct. Mater. **25**, 1270–1278 (2015)
61. J. Luo, J. Yang, X. Zheng, X. Ke, Y. Chen, H. Tan, J. Li, A highly stretchable, real-time self-healable hydrogel adhesive matrix for tissue patches and flexible electronics. Adv. Healthc. Mater. **9**, 1901423 (2020)
62. X. Ke, Z. Dong, S. Tang, W. Chu, X. Zheng, L. Zhen, X. Chen, C. Ding, J. Luo, J. Li, A natural polymer based bioadhesive with self-healing behavior and improved antibacterial properties. Biomater. Sci. **8**, 4346–4357 (2020)
63. H. Fan, J. Wang, Q. Zhang, Z. Jin, Tannic acid-based multifunctional hydrogels with facile adjustable adhesion and cohesion contributed by polyphenol supramolecular chemistry. ACS Omega **2**, 6668–6676 (2017)
64. X. Fan, S. Wang, Y. Fang, P. Li, W. Zhou, Z. Wang, M. Chen, H. Liu, Tough polyacrylamide-tannic acid-kaolin adhesive hydrogels for quick hemostatic application. Mater. Sci. Eng. C **109**, 110649 (2020)
65. J. Wen, X. Zhang, M. Pan, J. Yuan, Z. Jia, L. Zhu, A robust, tough and multifunctional polyurethane/tannic acid hydrogel fabricated by physical-chemical dual crosslinking. Polymers **12**, 239 (2020)
66. K. Kim, M. Shin, M.-Y. Koh, J.H. Ryu, M.S. Lee, S. Hong, H. Lee, TAPE: a medical adhesive inspired by a ubiquitous compound in plants. Adv. Funct. Mater. **25**, 2402–2410 (2015)
67. S. Jin, S. Kim, D.S. Kim, D. Son, M. Shin, Optically anisotropic topical hemostatic coacervate for naked-eye identification of blood coagulation. Adv. Funct. Mater. **32**, 2110320 (2022)
68. S. Hao, C. Shao, L. Meng, C. Cui, F. Xu, J. Yang, Tannic acid-silver dual catalysis induced rapid polymerization of conductive hydrogel sensors with excellent stretchability, self-adhesion, and strain-sensitivity properties. ACS Appl. Mater. Interfaces **12**, 56509–56521 (2020)
69. J. Guo, W. Sun, J.P. Kim, X. Lu, Q. Li, M. Lin, O. Mrowczynski, E.B. Rizk, J. Cheng, G. Qian et al., Development of tannin-inspired antimicrobial bioadhesives. Acta Biomater. **72**, 35–44 (2018)
70. H. Qiao, P. Qi, X. Zhang, L. Wang, Y. Tan, Z. Luan, Y. Xia, Y. Li, K. Sui, Multiple weak H-bonds lead to highly sensitive, stretchable, self-adhesive, and self-healing ionic sensors. ACS Appl. Mater. Interfaces **11**, 7755–7763 (2019)
71. K. Guk, G. Han, J. Lim, K. Jeong, T. Kang, E.-K. Lim, J. Jung, Evolution of wearable devices with real-time disease monitoring for personalized healthcare. Nanomaterials **9**, 813 (2019)